

**6.09 NIVOLUMAB plus IPILIMUMAB,  
NIVOLUMAB: Injection concentrate for I.V. infusion  
100 mg in 10 mL, Injection concentrate for I.V.  
infusion 40 mg in 4 mL,  
OPDIVO®;  
IPILIMUMAB: Injection concentrate for I.V. infusion  
200 mg in 40 mL, Injection concentrate for I.V.  
infusion 50 mg in 10 mL,  
YERVOY®;  
Bristol-Myers Squibb Australia Pty Ltd**

**1 Purpose of submission**

- 1.1 The Category 2 submission requested the PBS restrictions for nivolumab (NIVO) combined with ipilimumab (IPI; NIVO + IPI) be expanded to allow the treatment of unresectable Stage III or IV malignant melanoma in patients who experience melanoma recurrence while receiving or within 6 months of completing adjuvant anti-programmed cell death protein 1 (hereafter, PD-1 inhibitor) monotherapy.
- 1.2 Listing in the expanded population of patients who have previously received adjuvant PD-1 monotherapy and then recurred on treatment or within 6 months was requested at the current approved ex-manufacturer prices (AEMPs) for NIVO and IPI in the unresectable Stage III or IV malignant melanoma patient population. The request was made based on superiority in clinical efficacy compared to IPI monotherapy and BRAF inhibitors (BRAFi) therapy in the adjuvant PD-1 inhibitor pre-treated population.
- 1.3 Table 1 summarises the components of the overall clinical claim addressed by the submission.

**Table 1: Key components of the clinical issue addressed by the submission**

Component	Description
Population	Patients diagnosed with Stage III or IV unresectable malignant melanoma who have experienced melanoma recurrence while receiving adjuvant PD-1 inhibitor OR melanoma recurrence within 6 months of completion of adjuvant PD-1 inhibitor treatment
Intervention	Nivolumab in combination with ipilimumab (NIVO + IPI)
Comparator	Main: Ipilimumab (IPI) Secondary: BRAF inhibitor (BRAFi)
Outcomes	OS, PFS, ORR, RFS, DMFS, adverse events
Clinical claim	Main comparison: NIVO + IPI vs IPI NIVO + IPI is superior in terms of effectiveness and inferior in terms of safety compared with IPI. Secondary comparison: NIVO + IPI vs BRAFi NIVO + IPI has improved effectiveness and inferior safety compared with BRAFi.

Source: Table 1, p13 of the submission.

BRAFi = B-raf inhibitor; DMFS = distant metastasis free survival; IPI = ipilimumab; NIVO = nivolumab; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PD-1 = programmed death-1; RFS = recurrence free survival.

## 2 Background

### **Registration status**

2.1 NIVO + IPI combination was approved by the TGA on 4 July 2018 for the following indications:

- “ipilimumab, in combination with nivolumab, is indicated for the treatment of patients with unresectable or metastatic melanoma.”
- “nivolumab, in combination with ipilimumab, is indicated for the treatment of patients with unresectable or metastatic melanoma.”

This was consistent with the requested PBS listing for NIVO + IPI in this submission.

2.2 NIVO + IPI combination therapy has been approved in the USA, EU, Canada, and Switzerland with no restrictions specific to the retreatment of melanoma after adjuvant PD-1 inhibitor therapy.

### **Previous PBAC consideration**

2.3 NIVO + IPI combination therapy is currently listed on the PBS for the treatment of Stage III or Stage IV malignant melanoma. In November 2019, the PBAC indicated that it “...would be willing to review the six-month recurrence-free interval for retreatment if data was provided that supported the efficacy and cost-effectiveness of retreatment...” (paragraph 3.4, nivolumab Public Summary Document (PSD), November 2019).

### 3 Requested listing

Medicine	Treatment phase	Clinical criteria (strikethrough = deletion, italics = addition)
NIVO  PBS codes: 11532Y 11543M	Induction	<p>Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for the treatment of unresectable Stage III or Stage IV malignant melanoma, AND  <del>Patient must not have experienced disease progression whilst on adjuvant PD-1 inhibitor treatment or disease recurrence within 6 months of completion of adjuvant PD-1 inhibitor treatment if treated for resected Stage IIIB, IIIC, IIID or IV melanoma,</del>  AND  Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1,  AND  The condition must not be ocular or uveal melanoma,  AND  The treatment must be in combination with PBS-subsidised treatment with ipilimumab as induction for this condition.</p>
NIVO  PBS codes: 10745M 10748Q	Maintenance	<p>Patient must have previously received of up to maximum 4 doses of PBS-subsidised combined therapy with nivolumab and ipilimumab as induction for this condition,  AND  The treatment must be as monotherapy for this condition,  AND  Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for <del>this condition.</del> the treatment of unresectable Stage III or Stage IV malignant melanoma.</p>
IPI  PBS codes: 2638W 2641B	Induction	<p>Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for the treatment of unresectable Stage III or Stage IV malignant melanoma,  AND  <del>Patient must not have experienced disease progression whilst on adjuvant PD-1 inhibitor treatment or disease recurrence within 6 months of completion of adjuvant PD-1 inhibitor treatment if treated for resected Stage IIIB, IIIC, IIID or IV melanoma,</del>  AND  Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1,  AND  The condition must not be ocular or uveal melanoma,  AND  The treatment must be in combination with PBS-subsidised treatment with nivolumab as induction therapy for this condition.</p>

Source: Table 9, p35 of the submission.

- 3.1 The submission proposed removing the clinical criteria from the existing induction therapy listings for NIVO and IPI in the treatment of unresectable Stage III or IV malignant melanoma that prevent retreatment with PD-1 inhibitor-based therapy in patients who experienced disease recurrence in the adjuvant setting or within 6 months of completing adjuvant treatment.
- 3.2 The requested restrictions were consistent with the respective TGA indications and the evidence presented.
- 3.3 The submission noted that at the request of several Medical Oncologists, a Patient Access Program - the Opdivo Melanoma Continuation Program (OMCP) - was opened in November 2020 across 62 hospitals. As of June 2022, < 500 patients had

enrolled in the program with an estimated < 500 patients actively receiving treatment. The submission projected that at the time of PBS listing, < 500 patients would be eligible to transition to PBS-subsidised therapy.

- 3.4 Therefore, a request for grandfather restrictions for the NIVO induction and maintenance treatment phases was presented to enable patients to switch from non-PBS subsidised therapy via the OMCP to PBS-subsidised therapy. The submission stated that a grandfather restriction would not be required for the IPI induction treatment phase.
- 3.5 It was not anticipated that there would be flow-on changes to other PBS listed medicines (e.g. pembrolizumab (PEMBRO) or NIVO monotherapy) for this indication. The ESC noted that as this submission does not include PD-1 inhibitor monotherapy, patients will not be able to access PEMBRO or NIVO monotherapy if they experience disease progression whilst on, or within 6 months of completing, adjuvant PD-1 inhibitor treatment.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **4 Population and disease**

- 4.1 Australia and New Zealand have the highest incidence and mortality rates from melanoma in the world<sup>1</sup>. It has been estimated that the incidence of melanoma was 16,878 new cases in 2018, with 1,315 deaths<sup>2</sup>. Based on 2011-2016 data, the overall 5-year survival rate of patients diagnosed with Stage III and IV melanoma was approximately 61.1% and 26.2%, respectively<sup>3</sup>.
- 4.2 The target population includes patients who are currently ineligible to receive PD-1 inhibitor treatment for Stage III or IV malignant melanoma due to their prior exposure to PD-1 inhibitors in the adjuvant setting. These patients have experienced disease recurrence while receiving adjuvant PD-1 inhibitor treatment or melanoma recurrence within 6 months of completion of adjuvant PD-1 inhibitor treatment.
- 4.3 Figure 1 illustrates the current and proposed treatment options for patients diagnosed with “unresectable Stage III or IV malignant melanoma” and the impact of prior adjuvant therapy on the treatments available to patients. BRAF-WT patients can receive IPI monotherapy and BRAF-MT patients can receive either IPI monotherapy or BRAFi treatment. The submission proposed that NIVO + IPI be

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<sup>1</sup> Cancer Australia, (2021), Melanoma of the skin, <https://www.canceraustralia.gov.au/cancer-types/melanoma/statistics>

<sup>2</sup> Australian Institute of Health and Welfare (AIHW), (2021), Cancer data in Australia, <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-summary-data-visualisation>

<sup>3</sup> National Cancer Control Indicators, (2019), Relative survival by stage at diagnosis (melanoma), <https://ncci.canceraustralia.gov.au/outcomes/relative-survival-rate/relative-survival-stage-diagnosis-melanoma>

made available to both BRAF-WT and BRAF-MT patients who have received adjuvant PD-1 inhibitor monotherapy and experienced disease recurrence/progression while either receiving treatment or within 6 months of completing treatment.

- 4.4 No sources were cited for the current treatment algorithm provided in the submission. The submission stated that “Local treatment guidelines<sup>4</sup> and the National Comprehensive Cancer Network (NCCN) guidelines<sup>5</sup> do not make specific reference to the sequencing of adjuvant and metastatic systemic therapies.” The submission notes, however, that the European Society for Medical Oncology (ESMO) consensus conference recommendations for the management of metastatic melanoma<sup>6</sup> recommended that NIVO + IPI be included as a treatment option for BRAF-MT and BRAF-WT patients who have relapsed on PD-1 inhibitor treatment or within 6 months after completing treatment.
- 4.5 The ESC considered that the clinical algorithm presented was reasonable and was likely representative of the non-unidirectional and evolving nature of melanoma treatment in Australia.

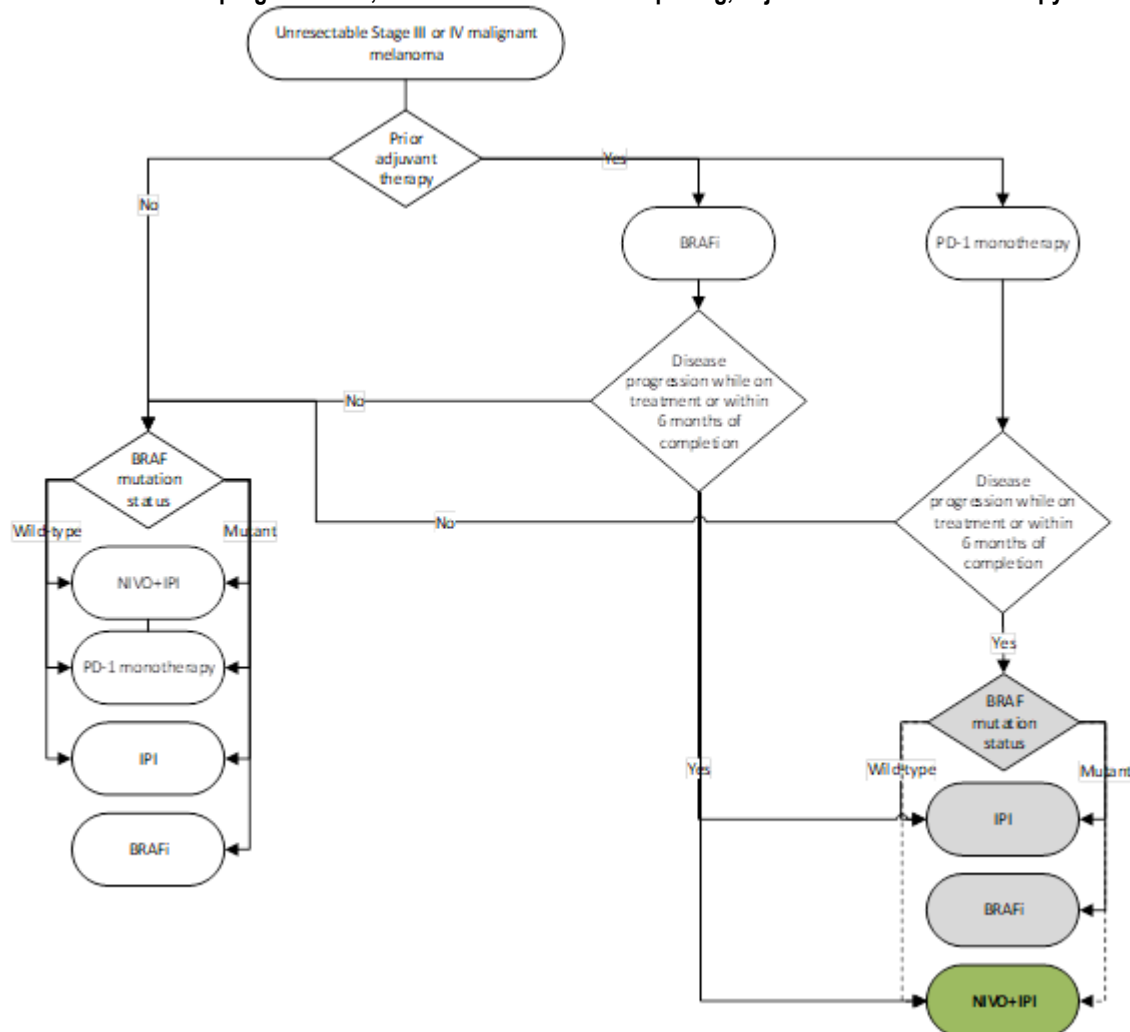
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<sup>4</sup> [Summary of recommendations and practice points: Immunotherapy for melanoma - Cancer Guidelines Wiki](#), accessed 25 March 2020

<sup>5</sup> [cutaneous\\_melanoma.pdf \(nccn.org\)](#), accessed 25 March 2020

<sup>6</sup> Keilholz et al, 2020, ESMO consensus conference recommendations on the management of metastatic melanoma: under the auspices of the ESMO Guidelines Committee. *Ann Oncol.* 2020 Nov; 31(11):1435-1448. doi: 10.1016/j.annonc.2020.07.004

Figure 1: Current (and proposed) treatment algorithm for patients with unresectable Stage III or IV malignant melanoma who have progressed on, or within 6 months of completing, adjuvant PD-1 inhibitor therapy



Source: Figure 8, p28 of the submission.

BRAFi = BRAF inhibitors; IPI = ipilimumab; NIVO = nivolumab; PD-1 = programmed death-1.

BRAF/MEK agents include: dabrafenib + trametinib, vemurafenib + cobimetinib, encorafenib + binimetinib.

For more detail on PBAC’s view, see section 7 PBAC outcome.

## 5 Comparator

5.1 The submission nominated IPI monotherapy as the main comparator and BRAFi as a secondary clinical comparator. The main arguments were that:

- IPI monotherapy is PBS-listed for both BRAF-WT and BRAF-MT patients in the metastatic setting. The submission estimated that 62.3% of patients have BRAF-WT and 37.7% have BRAF-MT. As most BRAF-MT patients that have received PD-1 inhibitor monotherapy in the adjuvant setting are eligible for BRAFi in the metastatic setting, the submission estimated that 6% of BRAF-MT patients would be eligible to receive IPI monotherapy treatment only. Therefore, it was

estimated that 65% of all patients can only receive IPI in the proposed setting, making IPI the predominant treatment available and the appropriate main clinical comparator.

The ESC considered that the nominated primary and secondary comparators were appropriate.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor submitted a clinician statement from key Australian opinion leaders in the field of melanoma medical oncology which strongly supported the submission.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (1), health care professionals (6) and organisations (2) via the Consumer Comments facility on the PBS website.
- 6.3 The input received from health professionals claimed that patients whose melanoma progresses on adjuvant therapy have better clinical outcomes on combination therapy (NIVO + IPI) than on IPI monotherapy, despite the increased incidence of adverse events. The comments stated that although adjuvant-resistant patients can receive combination therapy via compassionate access programs or clinical trials, the PBS listing of NIVO + IPI would significantly impact the lives of those in rural or remote areas. One health professional drew attention to the CT013 - S1616 randomised phase 2 trial which compared NIVO + IPI to IPI monotherapy after progression on PD1 inhibitor therapy<sup>7</sup>. Preliminary results presented at 2022 American Association for Cancer Research annual meeting demonstrated improvement in response rate and progression-free survival but no overall survival benefit for the combination versus monotherapy.
- 6.4 The input received from an individual undergoing NIVO + IPI treatment described the positive effects of treatment on disease progression and quality of life. While the individual experienced mild side effects, the input noted that the benefits of combination treatment outweighed the adverse events.
- 6.5 The Medical Oncology Group of Australia (MOGA) also expressed its support for the NIVO + IPI submission noting high unmet need and suggesting wider access on grounds of equity given international guidelines. The PBAC noted that the MOGA

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<sup>7</sup> Vandewalde AM, Moon J, Kendra K, et al. CT013 – S1616: ipilimumab plus nivolumab versus ipilimumab alone in patients with metastatic or unresectable melanoma that did not respond to anti-PD-1 therapy. AACR annual meeting 2022. Available at: [www.abstractsonline.com/pp8/#!/10517/presentation/20155](http://www.abstractsonline.com/pp8/#!/10517/presentation/20155)

presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for NIVO + IPI, which was limited to 2 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)<sup>8</sup>, based on a comparison with IPI monotherapy. The Melanoma & Skin Cancer Advocacy Network (MSCAN) also expressed its support for the NIVO + IPI submission.

### **Clinical studies**

6.6 The clinical data presented in the submission was sourced from two retrospective, cohort studies:

- da Silva et al (2021), for the main comparison versus IPI monotherapy. This was a non-randomised, multicentre, international, retrospective, cohort study, that included adults (18+ years) with unresectable Stage III or IV metastatic melanoma who were resistant to PD-1 inhibitor and who then received either IPI monotherapy or IPI plus PD-1 inhibitor (PEMBRO or NIVO).
- Owen et al (2020), for the secondary comparison versus BRAFi. This was a multicentre, international, retrospective, cohort study, that included patients with unresectable Stage III or IV metastatic melanoma who received at least one dose of adjuvant PD-1 inhibitor and experienced melanoma recurrence, who then received either (1) IPI monotherapy or (2) IPI plus PD-1 inhibitor or (3) BRAF/MEKi or (4) PD-1 inhibitor or (5) PD-(L)1 plus novel agent.

6.7 The submission relied on one other study, CheckMate 067 (also known as CA209-067 or CM-067, references: Larkins et al 2015, Larkins et al 2019, Wolchok et al 2021, Hodi et al 2022), as a basis for the proposed price in lieu of an economic analysis and in sensitivity analyses for treatment doses and duration when assessing the financial impacts. In CheckMate 067, patients with previously untreated advanced melanoma were randomised to receive NIVO + IPI induction followed by NIVO maintenance, or NIVO + IPI-matched placebo, or NIVO-matched placebo + IPI, and followed up for at least 60 months.

- CheckMate 067 has a different treatment population from the target population of the submission. Therefore, it was appropriately excluded as a study that provides clinical evidence in the submission.
- CheckMate 067 provided the clinical evidence for the listing of NIVO + IPI combination therapy for patients with unresectable Stage III and IV melanoma (NIVO PSD, November 2019).

6.8 The studies used to provide clinical evidence in the submission are described in Table 2 and

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<sup>8</sup> Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

6.9 Table 3. Both studies were non-randomised cohort studies and therefore at a high risk of bias. Although there was a high risk of selection bias, performance bias and detection bias found in the studies, the magnitude and direction of the biases could not be determined.

**Table 2: Studies presented in the submission**

Study identifier	Key data sources: Clinical Study Reports or key publication	Publication citation
Da Silva et al. (2021)	Ipilimumab alone or ipilimumab plus anti-PD-1 therapy in patients with metastatic melanoma resistant to anti-PD-(L)1 monotherapy: a multicentre, retrospective, cohort study.	Lancet Oncol 2021; 22 (6): 836-847. <a href="https://doi.org/10.1016/S1470-2045(21)00097-8">https://doi.org/10.1016/S1470-2045(21)00097-8</a>
Owen et al. (2020)	Management of early melanoma recurrence despite adjuvant anti-PD-1 antibody therapy.	Annals Oncol 2020; 31 (8): 1075-1082. <a href="https://doi.org/10.1016/j.annonc.2020.04.471">https://doi.org/10.1016/j.annonc.2020.04.471</a>

Source: Table 17, p41 of the submission, and text and references in the supplementary information.

**Table 3: Key features of the included studies**

Trial	Design/Duration	Risk of bias	Patient population	Key outcomes
Da Silva et al (2021)	Non-randomised, retrospective, cohort study  Study Duration: 2011-2020	High	Total: 355 - IPI monotherapy: 162 - IPI + PD-1 inhibitor: 193  44/355 patients experienced recurrence after adjuvant PD-1 inhibitor treatment. - IPI monotherapy: 8 - IPI + PD-1 inhibitor: 36	Overall survival Progression-free survival 1-year overall survival Objective response rate Disease control rate Proportion of treatment-related grade 3-5 adverse events
Owen et al (2020)	Non-randomised, retrospective, cohort study  Study Duration: 2015-2018	High	Total: 108 patients with cutaneous melanoma and unresectable loco-regional recurrence or initial or subsequent distance (of 147 patients treated with adjuvant PD-1 inhibitor, either mono or combination therapy, and experienced recurrence), received the following treatments: - IPI: 35 - BRAF/MEKi: 32 - PD-1 inhibitor: 16 - Local therapy: 22 - Not reported: 3  Of which, selected efficacy results were reported for: IPI±PD-1 inhibitor: 44, including: - IPI + PD-1 inhibitor: 31 - IPI monotherapy: 13 PD-1 monotherapy: 14 BRAFi monotherapy: 40 PD-(L)1 inhibitor + novel agent: 11	Overall survival Progression-free survival 1-year progression on-free survival Objective response rate Progressive disease Disease control rate

Source: Table 24, p61, table 27, p63 and table 30, p70 of the submission, and table S8, S9 and S10 in the supplementary information by da Silva et al (2021) and table S2 and S4 in the supplementary information by Owen et al (2020).

BRAFi/MEKi = BRAF inhibitor/MEKi inhibitor; IPI = ipilimumab; PD-(L)-1 = programmed death 1.

6.10 In both studies, the relevant patients (i.e. those who had progressed while receiving or within 6 months of receiving, PD-1 inhibitor monotherapy in the adjuvant setting) comprised small subgroups within the study populations.

- In da Silva et al (2021), the study population included all patients with unresectable Stage III or IV melanoma resistant to a PD-1 inhibitor, of which 44 patients received and developed resistance to PD-1 inhibitor therapy in the adjuvant setting. In this sub-group, 36/44 received IPI + PD-1 inhibitor treatment and 8/44 received IPI monotherapy. The remainder (311/355) developed resistance in the metastatic setting and were not relevant to the submission. The Pre-Sub-Committee Response stated that as there was no biological basis for there to be difference between adjuvant or metastatic anti-PD-1 resistance, and therefore asserted that the positive results shown in da Silva et al (2021) should be applicable across both settings.
- In Owen et al (2020), the study population consisted of patients who were exposed to and developed resistance to adjuvant PD-1 inhibitors. These patients then received IPI monotherapy, PD-1 inhibitor monotherapy, IPI + PD-1 inhibitor combination therapy, or BRAFi or PD-1 inhibitor + novel therapies. The submission presented the combined results for patients who received IPI ± PD-1 versus those who received BRAFi as the basis for the clinical comparison between IPI + PD-1 inhibitor versus BRAFi. Since the IPI ± PD-1 inhibitor group (N=44) contained 13 patients on IPI monotherapy (or 30%), use of this group as a proxy for the submission’s intervention (i.e. IPI + PD-1 inhibitor) was not appropriate.

6.11 In both studies, progressive disease (resistance criterion) was defined according to the Response Evaluation Criteria in Solid Tumours (RECIST) (version 1.1), by clinical estimation, without confirmatory scans to exclude potential pseudo progressions. This was appropriate.

6.12 The treatment details of the included studies are shown in Table 4.

**Table 4: Interventions compared in the studies**

Study	Treatment	Dosage regimen	Duration of treatment	Duration of follow-up
Da Silva et al (2021)	PEMBRO + IPI	2 mg/kg + 3 mg/kg (n=1)	Not reported	Median 22.1 months (IQR: 9.5, 30.9)
	NIVO + IPI	1 mg/kg + 3 mg/kg (n=192)		
	IPI monotherapy	3 mg/kg Q3W (n=112) 250 mg Q3W (n=50)		
Owen et al (2020)#	IPI + PD-1 inhibitor	Not reported (n=31)	Not reported	Median 7.7 months (Range: 0.2, 33.6)
	PD-1 inhibitor monotherapy	Not reported (n=13)		
	BRAFi	Not reported (n=40)		
	IPI monotherapy	Not reported (n=14)		
	PD-1 inhibitor + novel agent*	Not reported (n=11)		

Source: Table 18 and pp24-45, p56 of the submission

BRAFi = BRAF inhibitor; IPI = ipilimumab; IQR = interquartile range; NIVO = nivolumab; PD-1 inhibitor = anti-programmed death 1; PEMBRO = pembrolizumab.

\* PD-1 inhibitor + novel agents included: PD-1 inhibitor + LAG-2, PD-1 inhibitor + MEKi, PD-1 inhibitor + TLR9-agonist and PD-1 inhibitor + IDO1

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# There were inconsistencies in how Owen et al (2020) reported the number of patients in each treatment arm. This was also noted the submission (p57).

- 6.13 The doses and treatment frequency of IPI + PD-1 inhibitor and IPI monotherapy in da Silva et al (2021) were consistent with the dosages of NIVO + IPI proposed in the submission. Owen et al (2020) did not report the dosage regimens used.
- 6.14 The treatment duration was not reported in either study. The studies only reported the recurrence time after treatment. The submission stated that it used treatment duration estimates based on the patient access program, the OMCP (see paragraph 3.3), for the financial impact calculations.
- 6.15 Overall, the baseline characteristics of da Silva et al (2021) and Owen et al (2020) and the OMCP displayed some heterogeneity between the respective treatment groups. For example, the median age of patients receiving IPI monotherapy in da Silva et al (2021) was 6 years higher than those receiving IPI + PD-1 inhibitor. da Silva et al (2021) also reported differences between the arms in terms of Eastern Cooperative Oncology Group Scores, BRAF status and site of metastases. Patients appeared to differ in Owen et al (2020) in terms of median age, BRAF status, stage of disease and the adjuvant therapy received.

### ***Comparative effectiveness***

- 6.16 The results of the studies are shown in Table 5 (overall results from both da Silva et al 2021 and Owen et al 2020) and Table 6 (subgroup analysis from da Silva et al 2021). It was noted that:
- Only 44/355 patients in da Silva et al (2021) experienced recurrence after adjuvant PD-1 inhibitor treatment. This subgroup was directly relevant to the proposed listing in the submission; that is, patients with unresectable Stage III and IV melanoma who were exposed to adjuvant PD-1 inhibitor monotherapy and who developed resistance during treatment or within 6 months of treatment completion. The results from the relevant subgroup are presented in Table 6 (grey columns). The ESC considered that the subgroup results should be interpreted with caution due to the small sample size.
  - Owen et al (2020) presented combined results for the IPI monotherapy group and IPI + PD-1 inhibitor group (IPI ± PD-1 inhibitor) versus BRAFi (see Table 3). This combined group was not the same as the submission's proposed comparator (IPI + PD-1 inhibitor). Accordingly, the ESC considered that the results should be interpreted with caution. Additionally, the sample size was small (44 patients in IPI ± PD-1 inhibitor versus 40 patients in the BRAFi group) and the follow-up time was limited (5.5 to 8.4 months), resulting in high uncertainty in the overall survival outcomes. The ESC noted that the results for the subgroup of patients who more closely matched the proposed population (i.e. IPI + PD-1 inhibitor, n=31/44) were not presented in the submission.

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Table 5: Summary of key efficacy outcomes by treatment group (overall results)

	da Silva et al. (2021)			Owen et al. (2020) <sup>#</sup>	
	IPI + PD-1 inhibitor (n=193)	IPI (n=162)	p value	IPI ± PD-1 inhibitor <sup>a</sup> (n=44) **	BRAF <sup>i</sup> <sup>a</sup> (n=40)
<b>Median follow up</b>	22.1 months			7.7 months	
<b>Setting</b>	PD-1 inhibitor resistance in adjuvant and metastatic			PD-1 inhibitor resistance in adjuvant	
<b>OS</b>					
Median, months (95% CI)	20.4 (12.7, 34.8)	8.8 (6.1, 11.3)	-	21.3 <sup>c</sup> (17.6, NR)	12.3 <sup>c</sup> (8.7, NR)
HR (95% CI)	0.50 (0.38, 0.66)		<0.0001	NR	
6-month, % (95% CI)	~73 <sup>b</sup> (NR)	~58 <sup>b</sup> (NR)	-	NR	NR
12-month, % (95% CI)	58 (51, 66)	38 (31, 48)	-	NR	NR
<b>PFS</b>					
Median, months (95% CI)	3.0 (2.6, 3.6)	2.6 (2.4, 2.9)	0.0019	3.9 (2.7, 7.8)	10.7 (7.1, NR)
6-month, % (95% CI)	~35 <sup>b</sup>	~19 <sup>b</sup>	-	40 (26, 58)	70 (52, 93)
12-month, % (95% CI)	24 (19, 32)	12 (8, 19)	-	~25 <sup>b</sup>	~50 <sup>b</sup>
HR (95% CI)	0.69 (0.55, 0.87)		0.0019	NR	
<b>ORR, n (%)</b>					
ORR (CR + PR)	60 (31)	21 (13)	<0.0001†	10 (23)	27 (61)
CR	21 (11)	3 (2)	0.0002*	3 (7)	12 (30)
PR	39 (20)	18 (11)	-	7 (16)	15 (37.5)
SD	17 (9)	23 (14)	-	5 (11)	5 (12.5)
PD	116 (60)	118 (73)	-	23 (52)	1 (2.5)
Not reached	-	-	-	6 (14)	7 (17.5)
DCR (CR + PR + SD)	77 (40)	44 (27)	0.016†	15 (34)	32 (80)

Source: Table 27, pp62, 63 of the submission and Table 31, p70 of the submission.

BRAF<sup>i</sup> = BRAF inhibitor; CI = confidence interval; CR = complete response; DCR = disease control rate; HR = hazard ratio; IPI = ipilimumab; ORR = objective response rate; OS = overall survival; PD = progressive disease; PD-1 = programmed death-1; PFS = progression-free survival; PR = partial response; SD = stable disease

† Pearson's X2 test with Yates' correction

\* Pearson's X2 test

\*\* Includes one patient who was treated on a clinical trial with IPI, nivolumab and IDO-inhibitor and one treated with IPI + TLR9-agonist.

<sup>#</sup> There were inconsistencies in how Owen et al (2020) reported the number of patients in each treatment arm, which was also noted in the submission (p57). It might have been because not all patients were able to be evaluated.

<sup>a</sup> ORR total has been adjusted to reflect CR + PR as reported in Table S3 to match the reporting method for da Silva et al (2021) and allow naïve comparison across trials

<sup>b</sup> Value read from figure, not reported separately

<sup>c</sup> OS reported for first-line therapy only

**Table 6: Subgroup response results by prior PD-1 inhibitor in the adjuvant versus metastatic setting from the da Silva et al (2021) study**

	IPI + PD-1 inhibitor			IPI		
	Full cohort N=193	Prior PD-1 inhibitor in adjuvant setting N=36	Prior PD-1 inhibitor in metastatic setting N=157	Full cohort N=162	Prior PD-1 inhibitor in adjuvant setting N=8	Prior PD-1 inhibitor in metastatic setting N=154
ORR, n/N (%)	60/193 (31%)	13/36 (36%)	47/157 (30%)	21/162 (13%)	1/8 (13%)	20/154 (13%)
Median PFS, months (95% CI)	3.0 (2.6, 3.6)	3.3 (2.5, NR)	3.0 (2.3, 3.5)	2.6 (2.4, 2.9)	2.5 (1.8, NR)	2.6 (2.4, 2.9)
12-month PFS	24%	47%	22%	12%	25%	13%
Median OS, months (95% CI)	20.4 (12.7, 34.8)	NR	16.7 (10.7, 32.8)	8.8 (6.1, 11.3)	11.2 (9.2, NR)	8.5 (5.6-10.6)
12-month OS	58%	75%	55%	38%	38%	38%

Source: Table 30, p70 of the submission.

CI = confidence interval; IPI = ipilimumab; NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PD-1 = programmed death-1.

6.17 Results for the whole study population of da Silva et al (2021) (N=355) demonstrated that:

- overall survival (OS) was statistically significantly longer in the IPI + PD-1 inhibitor group (median 20.4 months; 95% CI: 12.7, 34.8) than in the IPI monotherapy group (median 8.8 months; 95% CI: 6.1, 11.3), with a hazard ratio (HR) of 0.50 (95% CI: 0.38, 0.66);
- progression-free survival (PFS) was statistically significantly longer in the IPI + PD-1 inhibitor group (median 3.0 months; 95% CI: 2.6, 3.6) than in the IPI group (median 2.6 months; 95% CI: 2.4, 2.9). The HR was 0.69 (95% CI: 0.55, 0.87); and
- the objective response rate (ORR) was higher with IPI + PD-1 inhibitor (31%) than with IPI monotherapy (13%).

6.18 The key observations highlighted in the submission for the relevant subgroup from da Silva (i.e., those who received adjuvant PD-1 inhibitor and developed resistance, N = 44) were:

- the treatment response (ORR) and the proportion of patients both progression-free (12 months PFS) and alive at 12 months (12 months OS) were greater in the IPI + PD-1 inhibitor subgroup, compared to the IPI monotherapy group (ORR: IPI + PD-1 inhibitor 36% versus IPI 13%; 12-month PFS: IPI + PD-1 inhibitor 47% versus IPI 25%; and 12-month OS: IPI + PD-1 inhibitor subgroup 75% versus IPI 38%);
- the data were immature as median OS for the IPI + PD-1 inhibitor subgroup was not reached. The median OS for the relevant IPI arm was 11.2 months (95% CI: 9.2, NR); and
- the subgroup analysis was underpowered as the study was not designed to detect the differences in clinical efficacy between IPI + PD-1 inhibitor versus IPI

monotherapy in the target group. Patient numbers in both arms of the subgroup were small (36 in IPI + PD-1 inhibitor arm versus 8 in IPI arm) meaning the reported results were highly uncertain.

- 6.19 Results from Owen et al (2020) demonstrated that:
- PFS was shorter in the IPI ± PD-1 inhibitor group (median 3.9 months; 95% CI: 2.7, 7.8) than in the BRAFi group (median 10.7 months; 95% CI: 7.1, NR);
  - OS was longer in the IPI ± PD-1 inhibitor group (median 21.3 months; 95% CI: 17.6, NR) than in the BRAFi group (median 12.3 months; 95% CI: 8.7, NR). The submission noted the contradicting trend between PFS and OS between IPI ± PD-1 inhibitor vs BRAFi, and that the positive PFS in the BRAFi treatment tended to not translate into OS; and
  - ORR was lower with IPI ± PD-1 inhibitor (23%) than with BRAFi monotherapy (61%).
- 6.20 The submission also presented an unanchored, side-by-side comparison of efficacy outcomes for adjuvant pre-treated patients who received NIVO + IPI retreatment from da Silva et al (2021) and the patient access program, the OMCP (see Table 8).
- 6.21 The submission highlighted the differences in characteristics between OMCP patients and those in da Silva et al (2021) - see Table 7. The patient characteristics of the relevant subgroups from da Silva et al (2021) were not compared with the OMCP patients.

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**Table 7: Differences in patient characteristics between the da Silva study and the OMCP patients**

Patient characteristic	da Silva et al (2021) (N = 355)	OMCP (n = 148)	Discussion
Median age	IPI + PD-1 inhibitor arm: 61 years IPI arm: 67 years	67 years	A typical Australian patient (as reflected in by the OMCP patients) might be older than the da Silva population.
Gender	Male = 64%	Male = 66%	-
BRAF status	WT and NRAS: 51.3% BRAF mutant: 29.3% NRAS: 19.4%	WT/non-V600: 64% BRAF mutant: 34%	Large differences in BRAF status between the studied population and the OMCP patients
Median time to recurrence after commencing PD-1 inhibitor monotherapy	IPI + PD-1 inhibitor arm: 2.9 months (IQR: 2.1, 6.7) IPI arm: 3.0 months (IQR: 2.5, 5.7)	5.5 months (Range: 0.3, 18.1)	Median time to recurrence was longer in the OMCP patients.  The submission noted the possible reasons: - earlier stage of disease at adjuvant treatment - higher proportion of complete surgical resection prior to adjuvant treatment or many other factors - more robust health in the Australian population
Adjuvant PD-1 monotherapy	100%	100%	-
Systemic therapy between PD-1 inhibitor and study treatment	16%	0%	The submission noted that the use of other systemic treatment between adjuvant PD-1 inhibitor and the study drugs was not associated with increased response or survival. This difference is unlikely to impact the assessment of clinical outcomes in an Australian setting.

Source: Table 35, pp77-78, and Table 36, p79 of the submission.

IPI = ipilimumab; IQR = interquartile range; NRAS = NRAS mutation; OMCP = Opdivo Melanoma Continuation Program; PD-1 = programmed death-1; WT = wild type.

**Table 8: Unanchored, side-by-side comparison of efficacy outcomes with IPI + PD-1 inhibitor treatment from patients in da Silva et al (2021) who had received adjuvant PD-1 inhibitor monotherapy\* and the OMCP**

	da Silva et al (2021) (n=36)	OMCP data (n=42)#
<b>Response, %</b>		
ORR (CR + PR)	36	47.6
CR	NR	16.7
PR	NR	31.0
SD	NR	7.1
PD	NR	45.2
<b>Progression-free survival</b>		
Median PFS, months (95% CI)	3.3 (2.5, NR)	4.93 (2.3, NR)
12-month PFS (%)	47%	48%
<b>Overall survival</b>		
Median OS, months (95% CI)	NR	17.7 (11.5, NR)
12-month OS (%)	75%	64%

Source: Table 34, p76 of the submission

CI = confidence interval; CR = complete response; IPI = ipilimumab; NR = not reported; OS = overall survival; PD = progressive disease; PD-1 inhibitor = anti-programmed death-1; PFS = progression-free survival; PR = partial response; SD = stable disease.

\* This subgroup of patients in da Silva et al (2021) were those who were treated with IPI + PD-1 inhibitor following treatment with a PD-1 inhibitor in the adjuvant setting and who developed resistance (36/44 patients; 8/44 patients received IPI).

# Outcome data was available for 42 patients in the OMCP.

## Comparative harms

6.22 The submission stated that the intervention (NIVO + IPI) and comparators (IPI or BRAFi) under analysis have been TGA registered and listed on the PBS for several years, and therefore, their safety profiles are well known to clinicians.

6.23 Adverse event data from da Silva et al (2021) is presented in Table 9. The following observations were noted:

- The proportion of treatment-related grade 3-5 adverse events was similar in the IPI + PD-1 inhibitor group (31%) versus in the IPI group (33%). The most frequent Grade 3-5 treatment-related adverse events (TRAE) reported were diarrhoea or colitis (12%) and elevated liver enzymes (12%).
- It was noted that patients in the IPI ± PD-1 inhibitor group did not seem to have worse toxicity outcomes than those in the IPI monotherapy group. This may have been because those with severe adverse events with PD-1 inhibitor monotherapy might not have been offered (or declined to use) further immunotherapy.

**Table 9: Summary of key adverse events in the da Silva et al. (2021)**

Adverse events	Ipilimumab plus PD-1 inhibitor group (n=193)					Ipilimumab group (n=162)				
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 3–5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 3–5
Number of patients with at least one adverse event	102 (53%)	42 (22%)	19 (10%)	0	59 (31%)	69 (43%)	50 (31%)	4 (2%)	1 (1%)	54 (33%)
Gastrointestinal	46 (24%)	27 (14%)	19 (10%)	0	46 (24%)	27 (17%)	43 (27%)	4 (2%)	1 (1%)	48 (30%)
Diarrhoea or colitis	38 (20%)	18 (9%)	5 (3%)	0	23 (12%)	14 (9%)	30 (19%)	2 (1%)	1 (1%)	33 (20%)
Increased alanine aminotransferase or aspartate aminotransferase	15 (8%)	11 (6%)	13 (7%)	0	24 (12%)	9 (6%)	13 (8%)	2 (1%)	0	15 (9%)
Nausea or vomiting	0	0	0	0	0	4 (2%)	0	0	0	0
Increased amylase or lipase	1 (1%)	0	1 (1%)	0	1 (1%)	0	2 (1%)	0	0	2 (1%)
Skin	42 (22%)	4 (2%)	0	0	4 (2%)	27 (17%)	2 (1%)	0	0	2 (1%)
Rash or pruritus	39 (20%)	3 (2%)	0	0	3 (2%)	27 (17%)	2 (1%)	0	0	2 (1%)
Vitiligo	3 (2%)	0	0	0	0	0	0	0	0	0
Bullous pemphigoid	0	1 (1%)	0	0	1 (1%)	0	0	0	0	0
Hypophysitis, hypothyroidism, or hyperthyroidism	30 (16%)	3 (2%)	0	0	3 (2%)	9 (6%)	2 (1%)	0	0	2 (1%)
Fatigue	14 (7%)	0	0	0	0	7 (4%)	0	0	0	0
Respiratory pneumonitis	10 (5%)	2 (1%)	0	0	2 (1%)	5 (3%)	1 (1%)	0	0	1 (1%)
Arthralgia or myalgia	10 (5%)	1 (1%)	0	0	1 (1%)	10 (6%)	1 (1%)	0	0	1 (1%)
Fever	8 (4%)	2 (1%)	0	0	2 (1%)	2 (1%)	0	0	0	0
Uveitis, iritis, or blepharoconjunctivitis	5 (3%)	1 (1%)	0	0	1 (1%)	2 (1%)	1 (1%)	0	0	1 (1%)
Nephritis	6 (3%)	0	0	0	0	1 (1%)	1 (1%)	0	0	1 (1%)
Nervous system	2 (1%)	3 (2%)	0	0	3 (2%)	0	1 (1%)	0	0	1 (1%)
Headache	1 (1%)	0	0	0	0	0	0	0	0	0
Peripheral neuropathy	1 (1%)	0	0	0	0	0	0	0	0	0
Encephalitis or meningitis	0	2 (1%)	0	0	2 (1%)	0	1 (1%)	0	0	1 (1%)
Guillain-Barré Syndrome	0	1 (1%)	0	0	1 (1%)	0	0	0	0	0
Anaemia or thrombocytopenia	0	1 (1%)	0	0	1 (1%)	0	1 (1%)	0	0	1 (1%)
Myocarditis	0	0	0	0	0	0	1 (1%)	0	0	1 (1%)

Source: Figure 14, pp68-69 of the submission

6.24 Owen et al (2020) did not present comprehensive safety information. Only discontinuation due to toxicity was reported with 55% (17/31) of patients receiving IPI ± PD-1 inhibitor and 38% (5/13) receiving IPI discontinued treatment due to toxicity. However, the submission presented an overall safety profile of dabrafenib plus trametinib as a proxy for BRAFi treatment. Very limited conclusions can be drawn from the presented information due to the unknown differences in patient characteristics, treatment settings and method of assessments.

### **Clinical claim**

6.25 The submission claimed for:

- NIVO + IPI versus IPI (main comparison): In patients who have experienced disease recurrence after adjuvant PD-1 inhibitor treatment, retreatment with NIVO + IPI is superior in terms of effectiveness and inferior in terms of safety compared with IPI.
- NIVO + IPI versus BRAFi (secondary comparison): In patients who have experienced disease recurrence after adjuvant PD-1 inhibitor treatment, retreatment with NIVO + IPI is superior in terms of effectiveness and inferior in terms of safety compared with BRAFi.

6.26 The ESC considered that the clinical claims were uncertain for the following reasons:

- Neither of included studies were designed to examine the comparative efficacy and safety outcomes of NIVO + IPI against IPI monotherapy or BRAFi in the target population of the submission.
- It was unclear how confounders that might affect the internal validity and the generalisation of the efficacy and safety outcomes were managed in both studies. For instance, the heterogeneity in baseline characteristics between treatment groups in terms of age, BRAF status or ECOG status might have affected the likelihood of receiving IPI + PD-1 inhibitor rather than IPI monotherapy or BRAFi.
- In da Silva et al (2021) only 44/355 patients matched the target population of the submission, of which 36 received IPI + PD-1 inhibitor and 8 received the comparator, IPI monotherapy. The subgroup sample size was small and underpowered, meaning the comparison of clinical efficacy was unreliable. The safety comparison presented was for the whole study population (N=355), not for the target population subgroup.
- In Owen et al (2020), the comparative results were presented for a pooled population of patients (n=44) re-treated with either IPI monotherapy or IPI + PD-1 inhibitor versus 40 patients re-treated with BRAFi. The patient group used to draw the clinical results therefore did not match the target population. In addition, there was no safety comparison between IPI + PD-1 inhibitor and BRAFi available.

- 6.27 In the context that the response rates for IPI + PD-1 inhibitor therapy in the treatment of melanoma are high relative to those with PD-1 inhibitor therapy for other tumour types and noting that it was unlikely that better quality data would become available, the PBAC considered that the claim that IPI + PD-1 inhibitor was superior in terms of comparative effectiveness compared to IPI monotherapy and BRAFi was likely to be reasonable, although the magnitude of benefit was highly uncertain.
- 6.28 The PBAC considered that the claim that IPI + PD-1 inhibitor was inferior in terms of comparative safety compared to IPI monotherapy or BRAFi was reasonable.

### **Economic analysis**

- 6.29 The submission did not present an economic evaluation. The submission stated that due to the limited available data from the relevant subgroup of da Silva et al (2021), a reliable cost effectiveness analysis comparing NIVO + IPI to IPI monotherapy was not possible.
- 6.30 Instead, the submission presented an unanchored, side-by-side comparison of the efficacy data for patients who received IPI + PD-1 inhibitor treatment from da Silva et al (2021) and the OMCP and from CheckMate 067, which was presented when NIVO + IPI was first PBS listed for unresectable Stage III or IV malignant melanoma (Table 10).
- 6.31 The submission concluded that the PFS and OS data at the 12-month timepoint was similar across the 3 patient populations. Therefore, the submission requested the current price for NIVO and IPI in unresectable Stage III or Stage IV malignant melanoma for the expanded population of patients who have previously received adjuvant PD-1 monotherapy and then recurred on treatment or within 6 months.

**Table 10: Unanchored side-by-side comparison of efficacy outcomes with IPI + PD-1 inhibitor treatment from patients in da Silva et al (2021), the OMCP and CheckMate 067**

	da Silva et al (2021) (n=36)	OMCP data (n=42)*	CheckMate 067 (n=314)
<b>Response, %</b>			
ORR (CR + PR)	36%	47.6%	57.6%
CR	NR	16.7%	17.2%
PR	NR	31.0%	41.7%
SD	NR	7.1%	11.5%
PD	NR	45.2%	23.6%
NR	NR	0	6.1%
<b>Progression-free survival</b>			
12-month PFS, %	47%	47.9%	50%
<b>Overall survival</b>			
12-month OS, %	75%	63.8%	73%

Source: Table 40, p 94 from the submission

CR = complete response; IPI = ipilimumab; NIVO = nivolumab; NR = not reported; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.

\* Outcome data was available for 42 patients in the OMCP.

- 6.32 The requested prices for NIVO and IPI are presented in Table 11 below.

**Table 11: Requested prices for NIVO and IPI in expanded pre-treated adjuvant patient population (per metastatic melanoma specific pricing)**

	<b>Nivolumab</b>	<b>Ipilimumab</b>
Circumstances of use	In combination with ipilimumab	In combination with nivolumab
Restriction	Unresectable Stage III or IV malignant melanoma	
Manner of administration	Intravenous infusion	
Form/strength	100 mg/10 mL injection, 10 mL vial 40 mg/4 mL injection, 10 mL vial	200 mg/40 mL injection, 40 mL vial 50 mg/10 mL injection, 10 mL vial
Maximum amount (units)	120 mg induction 480 mg maintenance	360 mg induction only
Proposed effective AEMP	100 mg vial: \$ 40 mg vial: \$	200 mg vial: \$ 50mg vial: \$
Proposed published AEMP	100 mg vial: \$1,972.91 40 mg vial: \$789.17	200 mg vial: \$22,503.70 50 mg vial: \$5,625.92
<b>Induction therapy</b>		
Effective DPMA		
Public hospital use	\$	\$
Private hospital use	\$	\$
Published DPMA		
Public hospital use	\$2,454.58	\$45,094.43
Private hospital use	\$2,529.36	\$45,766.14
<b>Maintenance therapy</b>		
Effective DPMA		
Public hospital use	\$	NA
Private hospital use	\$	
Published DPMA		
Public hospital use	\$9,557.05	NA
Private hospital use	\$9,731.26	

Source: Table 41, p96 of the submission.

AEMP = agreed ex-manufacturer price; DPMA = dispensed price for maximum amount; NA = not applicable.

### **Estimated PBS usage & financial implications**

- 6.33 This submission was not considered by DUSC.
- 6.34 The submission used an epidemiological approach to forecast the financial impact of the proposed expansion of the existing PBS listings for NIVO and IPI. The submission reported that listing the combination of NIVO + IPI would result in adjunctive treatment rather than substitution, that is, NIVO would be added to the existing IPI use, therefore there would be no change to the current IPI utilisation.
- 6.35 The budget impact forecast was based primarily on the Sponsor’s patient access program, the OMCP which included 62 hospitals across Australia. The use of the OMCP data to inform treatment dosage and duration was reasonable as it represented actual use in the Australia population. However, use of this data may have underestimated the eligible population as more patients may be eligible to access NIVO + IPI if it was listed on the PBS/RPBS.
- 6.36 The inputs and data sources used to calculate the predicted use and financial impact of extending the existing PBS restrictions of NIVO + IPI are summarised in Table 12.

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Table 12: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value	Source	Comment
<b>Eligible population</b>			
Growth rate	Years 1 to 6: 3%	Australian Institute of Health and Welfare estimate of the growth rate for the incidence of melanoma of 2.9% to 3.7%	Reasonable; however, no sensitivity analyses were conducted using the AIHW's estimated range of 2.9% to 3.7%.
Incident patients commencing NIVO + IPI	Year 1: ■ <sup>1</sup> Year 2: ■ <sup>1</sup> Year 3: ■ <sup>1</sup> Year 4: ■ <sup>1</sup> Year 5: ■ <sup>1</sup> Year 6: ■ <sup>1</sup>	OMCP enrolment from the Sponsor, estimated ■ <sup>1</sup> patients per month (on average) in 2022 (total of ■ <sup>1</sup> patients per annum). 3% growth rate for Year 1 was added (total of ■ <sup>1</sup> patients plus ■ <sup>1</sup> grandfathered patients).	May underestimate the number of patients who would receive NIVO + IPI on the PBS.
<b>Treatment utilisation</b>			
Scripts dispensed	Year 1: ■ <sup>2</sup> Year 2: ■ <sup>2</sup> Year 3: ■ <sup>2</sup> Year 4: ■ <sup>2</sup> Year 5: ■ <sup>2</sup> Year 6: ■ <sup>2</sup>	Induction doses: 3 doses of NIVO 1mg/kg, every 21 days Maintenance doses: 3 doses of NIVO 480mg, every 28 days.  Based on the 6-month average of doses received per patient within the OMCP.	Use of OMCP data was reasonable.
<b>Costs</b>			
NIVO induction	DPMA (Effective): Public: \$ ■ Private: \$ ■	Requested price	-
NIVO maintenance	DPMA (Effective): Public: \$ ■ Private: \$ ■	Requested price	-

Source: Table 42, p100 and Table 44, p105 of the submission

AEMP = agreed ex-manufacturer price; DPMA = dispensed price for maximum amount; IPI = ipilimumab; NIVO = nivolumab; OMCP = Opdivo Melanoma Continuation Program.

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5,000

6.37 The estimated utilisation and financial impact of expanding the NIVO (+IPI) restriction are presented in **Error! Reference source not found.**

6.38 Based on the OMCP data, the submission assumed patients received an average of 3 doses of NIVO induction and 3 doses of NIVO maintenance. The submission stated that as patients treated on the OMCP are able to access IPI via the PBS, there would be no change to the current IPI utilisation.

**Table 13: Estimated net cost of additional NIVO to the PBS/RPBS (effective price)**

	2023	2024	2025	2026	2027	2028
Eligible patients	1	1	1	1	1	1
<b>Total NIVO script numbers</b>	2	2	2	2	2	2
Total NIVO cost to the PBS/RPBS (\$)	3	3	3	3	3	3
Patient co-payment* (\$)	3	3	3	3	3	3
<b>Net NIVO cost to the PBS/RPBS (\$)</b>	3	3	3	3	3	3
Net cost to MBS (\$)	3	3	3	3	3	3
<b>Overall net cost (\$)</b>	3	3	3	3	3	3

Source: Section 4\_BIM\_Fst Recurrer.xlsx workbook

MBS = Medical Benefits Schedule; NIVO = nivolumab; PBS = Pharmaceutical Benefit Scheme; RPBS = Repatriation Pharmaceutical Benefit Scheme.

\* Average PBS co-payment = \$25.31, average RPBS co-payment = \$6.38

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5,000

<sup>3</sup> \$0 to < \$10 million

6.39 The submission estimated that expansion of the restriction would result in additional cost to the PBS/RPBS of approximately \$0 to < \$10 million in Year 1, \$0 to < \$10 million in Year 6 and a total of \$0 to < \$10 million over the first 6 years of listing. The net cost to the MBS increased due to the additional use of MBS item 13950 (parenteral administration of antineoplastic drugs).

6.40 The net cost of expanding the restriction was uncertain as uptake of NIVO + IPI on the PBS/RPBS may be higher than estimated by the OMCP.

### **Quality use of medicines**

6.41 The submission discussed the activities to support the quality use of medicines, including physician education, immuno-oncology preceptorship, peer-to-peer support, nursing and pharmacy in-services, and a risk management plan. The submission stated that the Sponsor has committed to continuing education/quality use of medicine initiatives.

### **Financial Management – Risk Sharing Arrangements**

6.42 The submission requested an increase to the current PD-1 inhibitor melanoma expenditure cap to accommodate the increased utilisation of NIVO in this setting. No further details were presented in the submission.

For more detail on PBAC's view, see section 7 PBAC outcome.

## **7 PBAC outcome**

7.1 The PBAC recommended expanding the listing of nivolumab in combination with ipilimumab (NIVO + IPI) to allow the treatment of Stage III or IV malignant melanoma in patients who experience melanoma recurrence while receiving or within 6 months of completing adjuvant PD-1 inhibitor monotherapy. The PBAC noted that the magnitude of benefit of NIVO + IPI in the proposed population was highly uncertain due to the low quality of the clinical evidence presented. The PBAC

considered that, although uncertain, the cost-effectiveness of NIVO + IPI as previously determined for patients with unresectable Stage III or IV malignant melanoma was unlikely to be substantially altered by inclusion of the expanded population. The PBAC considered these uncertainties were acceptable in the context of the modest financial impact and advised that the financial impact be managed through the existing PD-1 inhibitor melanoma risk sharing arrangement (RSA).

- 7.2 The PBAC noted the strong clinician support for the expansion of the metastatic melanoma listings for NIVO and IPI which was received via the clinician statement and the Consumer Comments facility.
- 7.3 The PBAC considered that the proposed restrictions for NIVO and IPI were reasonable. The PBAC considered that the grandfather restrictions for NIVO would be required to allow patients to transfer from the patient access program to the PBS, noting that the sponsor did not request such a restriction for the ipilimumab component of initial treatment.
- 7.4 The PBAC considered that the nominated comparators of IPI monotherapy and BRAF inhibitor (BRAFi) therapy were appropriate.
- 7.5 The PBAC noted that the submission presented data from two retrospective, cohort studies, da Silva et al (2021) and Owen et al (2020). The PBAC considered that the data presented was uncertain as:
- Neither study was designed to examine the comparative efficacy and safety of NIVO + IPI against the nominated comparators of IPI monotherapy (da Silva et al [2001]) or BRAFi (Owen et al [2020]) in the target population.
  - There was heterogeneity in the baseline characteristics between the treatment groups in terms of age, BRAF status and ECOG status which suggests treatment allocation may have been affected by these factors.
  - The number of patients in the applicable subgroup of da Silva et al (2021) was small (44/355). As 36 patients in the subgroup received IPI + PD-1 inhibitor and only 8 received IPI monotherapy, the comparison for clinical efficacy was unreliable.
  - In Owen et al (2020) results were presented for a pooled population of patients re-treated with either IPI monotherapy or IPI + PD-1 inhibitor (n=44) versus patients re-treated with a BRAFi (n=40). Therefore, the patient group used for the clinical comparison did not match the target population.
- 7.6 In the context that the response rates for IPI + PD-1 inhibitor therapy in the treatment of melanoma are high relative to those with PD-1 inhibitor therapy for other tumour types and noting that it was unlikely that better quality data would become available, the PBAC considered that the claim that IPI + PD-1 inhibitor was superior in terms of comparative effectiveness compared to IPI monotherapy and

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BRAF<sup>i</sup> was likely to be reasonable, although the magnitude of benefit was highly uncertain.

- 7.7 The PBAC considered that the claim that IPI + PD-1 inhibitor was inferior in terms of comparative safety compared to IPI monotherapy and BRAF<sup>i</sup> was reasonable.
- 7.8 The PBAC noted that the submission did not present an economic evaluation, instead requesting the current weighted approved ex-manufacturer prices (AEMPs) for NIVO and IPI in unresectable Stage III or Stage IV malignant melanoma for the expanded population of patients who have received adjuvant PD-1 monotherapy and then experienced recurrence. The PBAC considered that, although uncertain, the cost-effectiveness of NIVO + IPI in the expanded population was unlikely to be substantially different to that previously determined by the PBAC for patients with unresectable Stage III or IV malignant melanoma, and therefore that the current weighted AEMPs would be reasonable for the new population.
- 7.9 The PBAC considered that the assumption in the submission that there would be an increase in NIVO utilisation only, with no change in the utilisation of IPI, was reasonable and noted that the estimated utilisation and financial impact of expanding the NIVO restrictions would be modest (\$0 to < \$10 million over 6 years).
- 7.10 The PBAC noted that the submission requested an increase to the current PD-1 inhibitor melanoma expenditure caps to accommodate the increased utilisation of NIVO in this setting. The PBAC noted the Commonwealth payment for Year 1 (20/21) and Year 2 (21/22) was ██████% of the cap thresholds and that the rebate for use exceeding the caps was ██████%. In this context, the PBAC advised the risk associated with the modest financial impact of NIVO + IPI for the expanded population should be managed by including the expenditure for the expanded population in the existing PD-1 inhibitor melanoma expenditure caps.
- 7.11 The PBAC advised that because the expansion of the NIVO + IPI restriction was uncertain in terms of the magnitude of benefit and was not expected to address a high and urgent unmet clinical need given the presence of alternative therapies, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022 for Pricing Pathway A were not met.
- 7.12 The PBAC affirmed its previous advice that NIVO and IPI are not suitable for inclusion in the PBS medicines for prescribing by nurse practitioners/midwives within collaborative arrangements such as continuing therapy only/within a shared care model.
- 7.13 The PBAC advised that NIVO and IPI should not be exempt from the Early Supply Rule.
- 7.14 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

8.1 Amend the following PBS restrictions as indicated below:

**NIVO induction (for use in combination with IPI):**

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts
NIVOLUMAB Injection	11543M (Public) 11532Y (Private)	120 mg	3
<b>Available brands</b>			
Opdivo (nivolumab 40 mg/4 mL injection, 4 mL vial)			
Opdivo (nivolumab 100 mg/10 mL injection, 4 mL vial)			
<b>Amend Restriction Summary/ Treatment of Concept:</b>			
<b>Concept ID</b> (for internal Dept. use)	<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals		
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners		
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED)		
<b>Caution:</b> Combination treatment with ipilimumab and nivolumab is associated with an increased incidence and severity of immune-related adverse reactions compared with monotherapy with these agents. Monitoring at least prior to each dose is recommended.			
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.			
<b>Administrative Advice:</b> Special Pricing Arrangements apply.			
<b>Indication:</b> Unresectable Stage III or Stage IV malignant melanoma			
<b>Treatment Phase:</b> Induction treatment			
<b>Clinical criteria:</b>			
Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for the treatment of unresectable Stage III or Stage IV malignant melanoma			
<b>AND</b>			
<b>Clinical criteria:</b>			
<del>Patient must not have experienced disease progression whilst on adjuvant PD-1 inhibitor treatment or disease recurrence within 6 months of completion of adjuvant PD-1 inhibitor treatment if treated for resected Stage IIIB, IIIC, IIID or IV melanoma</del>			
<b>AND</b>			
<b>Clinical criteria:</b>			
Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1			
<b>AND</b>			
<b>Clinical criteria:</b>			
The condition must not be ocular or uveal melanoma			

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	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must be in combination with PBS-subsidised treatment with ipilimumab as induction for this condition
	<b>Prescribing Instructions:</b> Induction treatment with nivolumab must not exceed a total of 4 doses at a maximum dose of 1 mg per kg every 3 weeks.
	<b>Prescribing Instructions:</b> Induction treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks.

**NIVO maintenance (for use after NIVO + IPI induction):**

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	№. of Rpts
NIVOLUMAB Injection	10745M (Public) 10748Q (Private)	480 mg	11
<b>Available brands</b>			
Opdivo (nivolumab 40 mg/4 mL injection, 4 mL vial) Opdivo (nivolumab 100 mg/10 mL injection, 4 mL vial)			
<b>Amend Restriction Summary / Treatment of Concept:</b>			
<b>Concept ID</b> (for internal Dept. use)	<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals		
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners		
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED)		
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.		
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.		
	<b>Indication:</b> Unresectable Stage III or Stage IV malignant melanoma		
	<b>Treatment Phase:</b> Maintenance treatment		
	<b>Clinical criteria:</b>		
	Patient must have previously received of up to maximum 4 doses of PBS-subsidised combined therapy with nivolumab and ipilimumab as induction for this condition		
	<b>AND</b>		
	<b>Clinical criteria:</b>		
	The treatment must be as monotherapy for this condition		
	<b>AND</b>		
	<b>Clinical criteria:</b>		
	Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this <del>condition</del> <i>PBS indication</i>		
	<b>Prescribing Instructions:</b> Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks under a weight based or flat dosing regimen.		
	<b>Prescribing Instructions:</b> The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.		

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**NIVO induction (for use in combination with IPI) – grandfather:**

MEDICINAL PRODUCT Form		PBS item code	Max. Amount	No. of Rpts
NIVOLUMAB Injection		11543M (Public) 11532Y (private)	120 mg	3
<b>Available brands</b>				
Opdivo (nivolumab 40 mg/4 mL injection, 4 mL vial)				
Opdivo (nivolumab 100 mg/10 mL injection, 4 mL vial)				
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>				
Concept ID (for internal Dept. use)	<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners			
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED) [New Code]			
<b>Caution:</b> <i>Combination treatment with ipilimumab and nivolumab is associated with an increased incidence and severity of immune-related adverse reactions compared with monotherapy with these agents. Monitoring at least prior to each dose is recommended.</i>				
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.				
<b>Administrative Advice:</b> Special Pricing Arrangements apply.				
<b>Indication:</b> Unresectable Stage III or Stage IV malignant melanoma				
<b>Treatment Phase:</b> <i>Transitioning from non-PBS to PBS-subsidised supply - Grandfather arrangements for combination induction therapy</i>				
<b>Clinical criteria:</b>				
Patient <i>must</i> have <del>previously</del> received non-PBS subsidised <i>treatment with</i> nivolumab in combination with ipilimumab for this PBS indication prior to ( <del>date to be determined</del> ) [listing date]				
<b>AND</b>				
<b>Clinical criteria:</b>				
Patient must have <i>had</i> an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 <i>prior to commencing non-PBS-subsidised treatment</i>				
<b>AND</b>				
<b>Clinical criteria:</b>				
The condition must not be ocular or uveal melanoma				
<b>AND</b>				
<b>Clinical criteria:</b>				
<i>The treatment must be in combination with PBS-subsidised treatment with ipilimumab as induction therapy for this condition</i>				
<b>Prescribing Instructions:</b> Induction treatment with nivolumab must not exceed a total of 4 doses at a maximum dose of 1 mg per kg every 3 weeks.				
<b>Prescribing Instructions:</b> Induction treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks.				

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**NIVO maintenance (for use after NIVO + IPI induction) – grandfather:**

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts
NIVOLUMAB Injection	10745M (Public) 10748Q (Private)	480 mg	11
<b>Available brands</b>			
Opdivo (nivolumab 40 mg/4 mL injection, 4 mL vial)			
Opdivo (nivolumab 100 mg/10 mL injection, 4 mL vial)			
<b>Amend Restriction Summary [new] / Treatment of Concept: [new]</b>			
Concept ID (for internal Dept. use)	<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals		
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners		
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED) [New code]		
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.			
<b>Administrative Advice:</b> Special Pricing Arrangements apply.			
<b>Indication:</b> Unresectable Stage III or Stage IV malignant melanoma			
<b>Treatment Phase:</b> <i>Transitioning from non-PBS to PBS-subsidised supply - Grandfather arrangements for maintenance treatment</i>			
<b>Clinical criteria:</b>			
Patient must have previously received of up to maximum 4 doses of PBS-subsidised ipilimumab combined therapy with non-PBS-subsidised nivolumab as induction for this condition prior to <del>(date to be confirmed)</del> [listing date]			
<b>AND</b>			
<b>Clinical criteria:</b>			
The treatment must be as monotherapy for this condition			
<b>AND</b>			
<b>Clinical criteria:</b>			
Patient must not have developed disease progression while receiving <del>PBS-subsidised</del> treatment with this drug for this <del>condition</del> <i>PBS indication</i>			
<b>Prescribing Instructions:</b> Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks under a weight based or flat dosing regimen.			
<b>Prescribing Instructions:</b> The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.			

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**IPi induction (for use in combination with NIVO):**

<b>MEDICINAL PRODUCT Form</b>		<b>PBS item code</b>	<b>Max. Amount</b>	<b>No. of Rpts</b>
IPILIMUMAB Injection		2641B (Public) 2638W (Private)	360 mg	3
<b>Available brands</b>				
Yervoy (ipilimumab 50 mg/10 mL injection, 10 mL vial) Yervoy (ipilimumab 200 mg/40 mL injection, 40 mL vial)				
<b>Amend Restriction Summary / Treatment of Concept:</b>				
<b>Concept ID</b> (for internal Dept. use)	<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners			
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED)			
<b>Caution:</b> Combination treatment with ipilimumab and nivolumab is associated with an increased incidence and severity of immune-related adverse reactions compared with monotherapy with these agents. Monitoring at least prior to each dose is recommended.				
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.				
<b>Administrative Advice:</b> Special Pricing Arrangements apply.				
<b>Indication:</b> Unresectable Stage III or Stage IV malignant melanoma				
<b>Treatment Phase:</b> Induction treatment				
<b>Clinical criteria:</b>				
Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for the treatment of unresectable Stage III or Stage IV malignant melanoma				
<b>AND</b>				
<b>Clinical criteria:</b>				
<del>Patient must not have experienced disease progression whilst on adjuvant PD-1 inhibitor treatment or disease recurrence within 6 months of completion of adjuvant PD-1 inhibitor treatment if treated for resected Stage IIIB, IIIC, IIID or IV melanoma</del>				
<b>AND</b>				
<b>Clinical criteria:</b>				
Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1				
<b>AND</b>				
<b>Clinical criteria:</b>				
The condition must not be ocular or uveal melanoma				
<b>AND</b>				
<b>Clinical criteria:</b>				
The treatment must be in combination with PBS-subsidised treatment with nivolumab as induction therapy for this condition				
<b>Prescribing Instructions:</b>				
Induction treatment with nivolumab must not exceed a total of 4 doses at a maximum dose of 1 mg per kg every 3 weeks.				

	<b>Prescribing Instructions:</b> Induction treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks.
	<b>Prescribing Instructions:</b> The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.

***This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.***

## **9 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **10 Sponsor's Comment**

The Sponsor is pleased to receive the recommendation for this indication and is committed to making this treatment option available to melanoma patients.